In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 19-446V

(to be published)

A.F., Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Chief Special Master Corcoran Filed: October 11, 2022

Edward Kraus, Kraus Law Group, LLC, Chicago, IL, for Petitioner

Mitchell Jones, U.S. Department of Justice, Washington, DC, for Respondent.

DECISION DENYING ENTITLEMENT[1]

On March 26, 2019, A.F. filed a Petition under the National Vaccine Injury Compensation Program (the "Vaccine Program"[2]), alleging that as a result of receiving the human papillomavirus ("HPV") in December 2017, she developed Postural Orthostatic Tachycardia Syndrome ("POTS"). Petition (ECF No. 1) ("Pet.") at 1. After the filing of multiple expert reports, I set a schedule to rule on the record, and the matter is now fully briefed. Petitioner's

[1] This Decision will be posted on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Decision will be available to anyone with access to the internet**. As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the published Ruling's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen (14) days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the entire Decision will be available to the public in its current form. *Id.*

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (codified as amended at 42 U.S.C. §§ 300aa-10–34 (2012)) (hereinafter "Vaccine Act" or "the Act"). All subsequent references to sections of the Vaccine Act shall be to the pertinent subparagraph of 42 U.S.C. § 300aa.

Motion, filed Dec. 13, 2021 (ECF No. 37) ("Mot."); Respondent's Opposition Brief, filed Mar. 21, 2022 (ECF No. 42) ("Opp."); Petitioner's Reply Brief, filed Apr. 22, 2022 (ECF No. 43) ("Reply").

Having reviewed the record and all associated filings, I hereby deny an entitlement award. The theory that the HPV vaccine can cause POTS has been routinely rejected in numerous prior Program cases as lacking reliable scientific support sufficient to meet the preponderant burden of proof. Nothing offered in this case suggests new, or more persuasive grounds, for finding otherwise.

I. Factual Background

Vaccination and Initial Symptoms

A.F. was born on January 14, 1993. Ex. 1 at 1. She was 24 at the time of vaccination, and had been prescribed a "beta blocker"[3] to address feelings of anxiety. Ex. 3 at 1. On December 26, 2017, Petitioner saw her primary care provider ("PCP"), Janet Mullins, M.D., for an annual physical. *Id.* During this visit, Dr. Mullins advised A.F. to undergo vaccination for HPV, and she accordingly received her first HPV vaccine dose four days later (December 30, 2017) at a Walgreen's Pharmacy. Ex. 7 at 2. There is no record evidence of any immediate reaction or malaise-like symptoms.

A few days later (January 3, 2018), Petitioner hit her hip against the sink while washing dishes, began feeling dizzy, and eventually passed out. Ex. 2 at 3. After experiencing similar symptoms while in the shower the following day, A.F. decided to consult a physician. *Id*. She subsequently saw Jane McCort, M.D., an internist at the University of Michigan Health Services, on January 4, 2018. Ex. 2. at 3–6. After an assessment, Dr. McCort advised A.F. that she had likely experienced a vasovagal episode after hitting her hip, and further instructed A.F. to reach out if she was not feeling better by the next day. *Id*.

Petitioner returned to Dr. McCort the next day (January 5, 2018), complaining that her symptoms had not improved, and noting that she continued to suffer from lightheadedness despite her efforts to rest and to maintain proper intake of fluids and food. Ex. 2 at 13. A.F. also informed Dr. McCort that she had received her first dose of the HPV vaccine the week before. *Id*. Dr. McCort reviewed A.F.'s lab work and noted that the results evidenced borderline leukocytosis but were otherwise normal. *Id*. at 15. Additionally, Petitioner's blood pressure

[3] Beta blockers (also known as beta-adrenergic blocking agents) reduce blood pressure by blocking the effects of the hormone epinephrine, also known as adrenaline. They resultingly cause the heart to beat more slowly and with less force, lowering blood pressure, and can also widen veins and arteries for improved blood flow. Mayo Clinic, *Beta Blockers*, https://www mayoclinic.org/diseases-conditions/high-blood-pressure/in-depth/beta-blockers/art-20044522 (last visited Oct. 11, 2022).

readings did not raise concerns for orthostatic intolerance, although Dr. McCort observed a slightly-abnormal heart rate increase of twenty to thirty beats per minutes following positional changes. *Id*. Although Dr. McCort expressed uncertainty as to why Petitioner continued to feel unwell, she allowed for the possibility that a number of contributory factors—the HPV vaccine, anxiety about her current symptoms, or stress related to school—could be relevant. *Id*. Dr. McCort recommended that A.F. rest over the weekend, take extra care when standing, and return again should her symptoms not improve. *Id*.

Suspicion of POTS

Several days later (January 9, 2018), A.F. visited Dr. McCort a third time, reporting extreme fatigue, mental fogginess, and difficulty focusing. Ex. 2 at 21. She also stated she felt as though her heart rate was going up, and that she was having heart flutters. *Id*. Dr. McCort noted that A.F.'s orthostatic measures from the January 4th visit had suggested the presence of POTS, and speculated that an immune reaction to the HPV vaccine could be causal. *Id*. Dr. McCort advised the Petitioner to undergo additional testing for cardiac issues and POTS. *Id*. at 23. To that end, Dr. McCort ordered testing in which A.F. was fitted with a 48-hour Holter monitor[4] on January 12, 2018. Ex. 4 at 4. The monitor revealed a single instance of tachycardia during a period where Petitioner reported feeling lightheaded. *Id.* at 4–6; 18–20. A.F. also underwent an echocardiogram which indicated the presence of an elongated anterior mitral valve leaflet without prolapse. *Id*. at 4–6. However, the results were otherwise deemed normal. *Id.* at 6.

On January 17, 2018, Petitioner saw cardiologist Dr. Frank Pelosi. Ex. 4 at 39–40; Ex. 9 at 1–2. She provided Dr. Pelosi with her recent medical history, which included feeling lightheaded at times and occasional heart palpitations, although these events were not consistently correlated with each other. *Id.* Dr. Pelosi opined that Petitioner had suffered at least one instance of syncope, along with "a vague, but profound fatigue." *Id.* He acknowledged the HPV vaccine might be associated with her symptoms, although it was also possible that Petitioner's susceptibility to syncopal events might render her prone to their repetition. *Id.* Dr. Pelosi's treatment recommendations echoed what Dr. McCort had proposed (e.g., increase fluid intake, get sufficient rest, maintain a proper diet, etc.). *Id.*

Two days later, on January 19, 2018, Petitioner was seen in the Emergency Department at the University of Michigan due to complaints of lightheadedness, diaphoresis, and nausea. Ex. 4 at 52–55. By this point, Petitioner deemed her fatigue so profound that she had withdrawn from

[4] A Holter monitor is a portable electrocardiogram (ECG) that continuously records the electrical activity of the heart for 24 hours or longer. Johns Hopkins Medicine, *Holter Monitor*, https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/holter-monitor (last visited Oct. 11, 2022).

school for the semester. *Id.*[5] A physical examination, cortisol levels, and head CT scan all produced normal results, however, and A.F.b2 was discharged and advised to follow up with her PCP. *Id.*

The following week (on January 25, 2018), A.F. saw a different cardiologist— Marwan Bahu, M.D.—for an evaluation for syncope. Ex. 8 at 1–2. The medical history recounted Petitioner's recent symptoms, along with her receipt of the HPV vaccine—but it also noted an instance in which Petitioner had "a year ago fainted with needle stick." *Id.* at 1. Orthostatic readings taken in what appears to be a "sit-stand" test revealed an increase of only 20 bpm from sitting to standing (although from supine to sitting to standing was a larger range of 54 bpm), and Dr. Bahu took note of the prior Holter test findings as well, and the exam identified no other issues beyond reported dizziness. In light of all of these factors, Dr. Bahu proposed that Petitioner had experienced "syncope and collapse." *Id.* Petitioner was (again) advised to increase her salt and fluid intake and prescription medicine was contemplated in the event improvement did not occur. *Id.*

Further Efforts at Treatment

Six weeks later, on March 5, 2018, A.F. went to see neurologist Brent Goodman at a Mayo Clinic satellite office in Arizona. Ex. 1 at 1–2. It was reported at this time that Petitioner had developed symptoms of orthostatic intolerance beginning four days after receipt of the HPV vaccine. *Id.* Upon examination, Petitioner displayed signs of hypermobility, scoring eight out of nine on the Beighton[6] scoring system. *Id.*

Dr. Goodman opined that Petitioner was suffering from POTS as well as a hypermobile form of Ehlers-Danlos syndrome,[7] attributing the former to the vaccine. Ex. 1 at 2. He ordered autonomic testing and lab work, and recommended certain lifestyle measures. *Id.* Dr. Goodman also noted that Petitioner might be a good candidate for certain kinds of drug therapies. *Id.*

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[5] On January 22, 2018, Dr. McCort wrote a letter regarding Petitioner's request for a leave of absence from school. Ex 4 at 94–95. In it, she explained that a "medical condition" was interfering with A.F.'s ability to meet her academic obligations. *Id.* at 94. The letter did not, however, identify a cause of this alleged condition, and made no reference to the HPV vaccine.

[6] "Beighton Score Test" is defined as "a test that detects joint hypermobility syndrome. The test uses a nine-point scoring system that measures the flexibility of certain joints. A positive Beighton score means you likely have joint hypermobility syndrome. Joint hypermobility syndrome may indicate other health problems that need further testing." *Beighton Score Test*, Cleveland Clinic, https://my.clevelandclinic.org/health/diagnostics/24169-beighton-score (last visited Oct. 11, 2022).

[7] "Ehlers-Danlos syndrome" is defined as "a group of inherited disorders of connective tissue . . . [p]rominent manifestations include hyperextensible skin and joints, easy bruisability, and friability of tissues with bleeding and poor wound healing, with additional symptoms specific for individual types." *Ehlers-Danlos syndrome*, Dorland's Medical Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=110561 (last visited Oct. 11, 2022).

On March 13, 2018, A.F. underwent an autonomic reflex study, which included a QSART[8] and tilt table test.[9] Ex. 1 at 30. Although there was no evidence of generalized autonomic failure, the tilt testing revealed evidence of orthostatic intolerance with postural tachycardia. *Id*. at 47. Seeing Petitioner about two weeks later (on March 23, 2018), Dr. Goodman reviewed these results and deemed them consistent with POTS. *Id.* at 4, 45, 47. He took special note of the fact that Petitioner had experienced an episode of vasodepressor near-syncope toward the end of the tilt test. *Id.* Now, in addition to the previously-proposed lifestyle changes, Petitioner was also prescribed medication. *Id.*

Limited records were filed in this case for subsequent time periods. On June 7, 2019, A.F. again saw Dr. McCort, reporting continued fatigue, light headedness, and palpitations with some frequency. Ex. 16 at 20. She was referred to cardiology for follow-up regarding her POTS diagnosis. *Id.* In 2020, Petitioner underwent testing for eleven categories of autoantibodies, including many proposed in this case (as discussed in greater detail below) to be causal of some forms of POTS. *See* CellTrend Result Report, dated September 10, 2020, filed as Ex. 48 (ECF No. 20-1). Petitioner was negative for every single identified autoantibody except two - anti ETAR[10] and anti-Muscarinic Cholinergic Receptor-3 Antibodies—with her measured levels deemed "at risk" for both (although in each case the amounts measured were barely above what would have constituted a negative reading).[11]

[8] "Quantitative Sudomotor Axon Reflex Test" measures nerves that control sweating, and can assist in identifying whether an individual possesses a disorder of the autonomic nervous system. *QSART*, Cleveland Clinic, https://my.clevelandclinic.org/health/diagnostics/16398-quantitative-sudomotor-axon-reflex-test-qsart (last visited Sept. 30, 2022).

[9] A "tilt test" is a "measurement of various bodily responses while the patient is tilted to different angles on a tilt table, usually head up, such as monitoring of circulatory, cardiac, and neurologic responses." *Tilt test*, Dorland's Medical Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=113022&searchterm=tilt+test (last visited Sept. 27, 2022).

[10] Anti-ETAR antibodies are antibodies against the endothelin receptor. A. Hineno et al., *Autoantibodies Against Autonomic Nerve Receptors in Adolescent Japanese Girls after Immunization with Human Papillomavirus Vaccine*, 2 Annals of Arthritis and Clinical Rheumatology 1–6 (2019), filed as Ex. 82 (ECF No. 30-7), at 2. Endothelin is an amino acid polypeptide that acts as a potent vasoconstrictor, with the capability of affecting blood pressure. *Dorland's Illustrated Medical Dictionary* 614 (33d ed. 2020).

[11] Thus, the anti-ETAR antibodies were determined to be present at a level of 11.6 units/ml—below the 17 units/ml level to test positive, and only slightly above the 10 units/ml level to test negative. And the anti-Muscarinic Cholinergic Receptor-3 antibodies were present at a level of 6.5 units/ml, well below the 10.0 units/ml required to test positive. Ex. 48.

II. Expert Reports

A. *Petitioner's Expert – Mitchell Miglis, M.D.*

Dr. Miglis, a neurologist specializing in autonomic nervous system disorders, prepared three reports in support of Petitioner's claim. Report, filed as Ex. 17 on February 27, 2020 (ECF No. 16-1) ("Miglis First Rep."); Report, filed as Ex. 73 on November 30, 2020 (ECF No. 26-2) ("Miglis Second Rep."); Report, filed as Ex. 85 on September 16, 2021 (ECF No. 34-1) ("Miglis Third Rep.").

Dr. Miglis obtained his undergraduate and medical degrees from the University of North Florida. *See* Curriculum Vitae, filed as Ex. 47 on September 15, 2022 (ECF No. 45-1) ("Miglis CV") at 1. He is a Clinical Assistant Professor in the department of Neurology at Stanford University. Miglis CV at 1; Miglis First Rep. at 1. During his time in practice, he has managed over 300 patients with POTS. Miglis First Rep. at 1. Dr. Miglis is licensed to practice medicine in New York, Massachusetts, and California, and is board certified in neurology and sleep medicine. Miglis CV at 2; Miglis First Rep. at 1. Dr. Miglis has also lectured and published in peer-reviewed scientific literature on POTS and sleep disorders. Miglis CV at 2–7, 9–10; Miglis First Rep. at 1.

First Report

Dr. Miglis began with a discussion of POTS, deeming it generally "a disorder of the autonomic nervous system." Miglis First Rep. at 2. POTS is characterized by sustained tachycardia, or increased heart rate, upon a postural change (like standing), along with sustained orthostatic hypotension (a drop in blood pressure) leading to feelings of dizziness due to decreased blood flow to the brain. *Id.* at 2–3. POTS has many secondary associated symptoms (e.g., shortness of breath, fatigue), and is not coterminous with vasovagal syncope, even though the latter can be a symptom of POTS. *Id.*[12]

Dr. Miglis acknowledged that POTS has "no single established etiology." Miglis First Rep. at 3. Indeed, literature he offered maintains that it is often the product of "cardiovascular deconditioning (i.e., cardiac atrophy and hypovolemia[13])," which would not be prompted by an aberrant immune response. Q. Fu & B. Levine, *Exercise and Non-Pharmacological Treatment of POTS,* 215 Auton. Neurosci. 20 (2019), filed as Ex. 19 (ECF No. 46-2) ("Fu & Levine") at 21. But he maintained there existed reliable evidence associating it with autoimmunity as well. As a

[12] Although Dr. Miglis also defined Ehlers-Danlos syndrome and discussed its POTS associations, Petitioner has not alleged that her Ehlers-Danlos was vaccine-caused.

[13] "Hypovolemia" is defined as "abnormally decreased volume of blood circulating in the body." *Hypovolemia*, Dorland's Medical Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=24456&searchterm=hypovolemia (last visited Oct. 11, 2022).

general matter, some POTS patients reported a viral illness before their symptoms, and women (who as a group experience autoimmune disease more frequently) also make up a large percentage of POTS patients. Miglis First Rep. at 3.

More specifically, Dr. Miglis observed that several specific autoantibodies had been identified as present in individuals suffering from POTS. In particular, Dr. Miglis represented that "several publications" have discussed instances in which "autoantibodies to G-protein-coupled receptors (GPCRs)" were measures in POTS patients. Miglis First Rep. at 3. This included autoantibodies to adrenergic receptors associated with the "fight or flight" response within the sympathetic nervous system—a physiologic, non-voluntary response to stress that would implicate autonomically-controlled biologic functions like heart rate or blood pressure. *Id.* at 3–4; H. Li et al., *Autoimmune Basis for Postural Tachycardia Syndrome*, 3 J. Am. Heart Assoc. 1–10 (2014), filed as Ex. 30 (ECF No. 47-3) ("Li I"); A. Fedorowski et al., *Antiadrenergic Autoimmunity in Postural Tachycardia Syndrome*, 19 European Soc'y of Cardiology 1211–1219 (2017), filed as Ex. 31 (ECF No. 47-4) ("Fedorowski").

Li I's authors, operating from the hypothesis that (because POTS often followed a viral illness) it might be an autoimmune-mediated condition, tested the blood of 14 POTS patients, finding that they possessed specific autoantibodies that might interfere with receptor functioning, producing postural tachycardia by causing "an inability of the peripheral blood vessels to fully constrict on standing," or simply by enhancing/exaggerating the tachycardia response. Miglis First Rep. at 4; Li I at 2. However, it was also noted that the cause of the autoantibody production was unknown. Li I at 8. Fedorowski had also observed the anti-adrenergic autoantibody presence in the 17 POTS patients considered, and concluded it was likely they played a role in POTS's pathogenesis (although its authors noted that POTS likely had "multiple causes," and that for the "vast majority of patients" there was little concrete evidence upon which causation theories involving autoantibodies could be based). Fedorowski at 1217.

Although Dr. Miglis admitted that the studies he cited for this point were small in scale (deeming their conclusions "preliminary" as a consequence), he also stressed that their findings were not recent (noting specifically that Li I had first observed the potential association in 2014). Miglis First Rep. at 4. In fact, he observed that these autoantibodies had been associated with other kinds of autonomic dysfunction, such as general orthostatic hypotension. *See, e.g.*, X. Yu et al., *Autoantibody Activation of Beta-adrenergic and Muscarinic Receptors Contributes to an "Autoimmune" Orthostatic Hypotension: Reception Autoantibodies in Orthostatic Hypotension*, 6 J. Am. Soc'y Hypertension 40–47 (2012), filed as Ex. 36 (ECF No. 47-9) (finding several activating autoantibodies, based on blood testing for six individuals, capable of contributing to the pathophysiology of orthostatic hypotension).

More recently-published articles had reached comparable conclusions. *See, e.g.*, W. Gunning et al., *Postural Orthostatic Tachycardia Syndrome is Associated with Elevated G-Protein Coupled Receptor Autoantibodies*, 8 J. Am. Heart Assoc. 1–10 (2019), filed as Ex. 83 (ECF No. 30-8) ("Gunning"); H. Li et al., *Adrenergic Autoantibody-Induced Postural Tachycardia Syndrome in Rabbits*, 8 J. Am. Heart Assoc. 1– 9 (2019), filed as Ex. 38 (ECF No. 48-1) ("Li II"). Gunning, for example, observed high titers of autoantibodies similar to the kinds previously noted in a cohort of 55 POTS patients whose blood was tested. Gunning at 5. But although Gunning speculates that viral infections (or vaccination) *could* explain the presence of the relevant autoantibodies, it also stated that "[t]he significance of autoantibodies against the adrenergic . . . receptor . . . is unknown," Gunning at 7–8.[14]

Li II, utilizing an animal model, purports to show that immunization with the autoantibodies "induced a POTS-like phenotype in rabbits." Miglis First Rep. at 5; Li II at 7. Specifically, Li II's authors directly immunized eight rabbits with peptides from the relevant adrenergic receptors believed to be interfered with by autoantibodies, found that the rabbits on a tilt test displayed a POTS-like heart rate increase at six weeks post-vaccination. Li II at 6–7. But Li II's authors admitted that demonstrated cardiovascular changes had some problems when compared to humans, since rabbits are quadrupeds. *Id.* at 6, 8 ("[t]here are currently no animal models that exhibit the characteristic postural or cardiovascular manifestations of POTS seen in humans"). And the article acknowledged otherwise that "POTS is likely a heterogeneous disorder with more than one underlying pathophysiology." *Id.* at 1. Dr. Miglis ultimately admitted that these more recent studies still left it underdetermined whether the tested autoantibodies are likely *causative* of POTS or simply reflect "immune dysregulation" in response to POTS. Miglis First Rep. at 5.

Next, Dr. Miglis proposed how the HPV vaccine might be generally associated with POTS. He started by referencing a number of articles that are often cited in cases involving the HPV vaccine and claims it can cause dysautonomia. Miglis First Rep. at 5–6; S. Blitshteyn, *Postural Tachycardia Syndrome Following Human Papillomavirus Vaccination*, 21 Eur. J. Neurol. 135–39, 138 (2014), filed as Ex. 40 (ECF No. 48-3) ("Blitshteyn I"); T. Kinoshita et al., *Peripheral Sympathetic Nerve Dysfunction in Adolescent Japanese Girls Following Immunization with the Human Papillomavirus Vaccine*, 53 Internal Med. 2185–200, 2185 (2014), filed as Ex. 41 (ECF No. 48-4) ("Kinoshita"); L. Brinth et al., *Orthostatic Intolerance and Postural Tachycardia Syndrome as Suspected Adverse Effects of Vaccination against Human Papilloma Virus*, 33 Vaccine 2602–2605, 2603 (2015), filed as Ex. 42 (ECF No. 48-5) ("Brinth").

[14] As support for a vaccine-autoantibody association, Gunning references one article also filed in this case—S. Blitshteyn, *Autoimmune Markers and Autoimmune Disorders in Patients with Postural Tachycardia Syndrome (POTS)*, 24 Lupus 1364–1369, 1367 (2015), filed as Ex. 29 (ECF No. 47-2) ("Blitshteyn II").

But the deficiencies of these items of literature are fairly self-evident (as has been observed in prior decisions). Blitshteyn I, for example, is a six-patient case series report with explanatory analysis, but which sheds little light on the nature of how the HPV vaccine could cause POTS, since it only observes a temporal association for the sample patients. Blitshteyn I at 138. And (like some of the more recent articles referenced by Dr. Miglis) Blitshetyn I notes that POTS "may arise from various mechanisms and etiologies," with an autoimmune explanation as only one possible cause. *Id.*

Kinoshita involved a larger cohort (44 Japanese patients) but presented self-selection bias circumstances (since the cohort members specifically sought treatment, as Dr. Miglis noted, based on the *belief* their vaccination was causal of the symptoms they were then experiencing) and thus did not reflect randomly-chosen patients. Kinoshita at 2185–86. Moreover, the symptoms reported were wide-ranging, with only a subset involving the kind of orthostatic features common to POTS–and only 13 of the total sample of patients had received the HPV formulation at issue in this case. *Id.* at 2186. Finally, an unidentified subset of 14 patients who purportedly had displayed "sympathetic dysfunction" (although only four of these subjects met the criteria for POTS) were tested for autoantibodies comparable to what are alleged herein to be driving POTS in some cases—and all were negative for them. *Id.* at 2194, 2199.

Brinth also relied on self-selected cohort populations. Brinth at 2603. There, 35 females "consecutively referred to our syncope unit," and based on a suspicion of an HPV vaccine-associated adverse event, were evaluated. *Id.* While the majority of them (60 percent) were found to meet the diagnostic criteria for POTS, no connection between vaccination and symptoms beyond a mere temporal association was observed, and indeed Brinth's authors noted that "[o]ur findings do not confirm or dismiss a causal link to the HPV vaccine." *Id.* at 2604.

Dr. Miglis himself ultimately admitted that these kinds of case series were "relatively small and admittedly observational," but he deemed them the next-best alternative to an absence of large-scale independent studies. Miglis First Rep. at 6. As an example of a purportedly *non-independent* study, he referenced an otherwise large-scale observational study that has often been discussed in cases involving the HPV vaccine. *Id.*; C. Chao et al., *Surveillance of Autoimmune Conditions following Routine Use of Quadrivalent Human Papillomavirus Vaccine*, 271 J. Intern. Med. 193–203, 202, (2012), filed as Ex. 44 (ECF No. 48-7) ("Chao") (following administration of the HPV4 vaccination in routine clinical use, no safety signal for a variety of autoimmune conditions existed within a large and mostly female population). Chao considered more than 180,000 instances of administration of an HPV vaccine dose in a patient sample which was almost wholly (99 percent) made up of women aged 9–26, although it did not explicitly look for POTS or instances of purported autoimmune-caused dysautonomia. Dr. Miglis nevertheless deemed the fact that Chao was funded by a pharmaceutical company to cast doubt on its veracity, given the inherent conflict of interest. Miglis First Rep. at 6.

Dr. Miglis also referenced an article that relied on an online survey to suggest an HPV vaccine-POTS relationship. Miglis First Rep. at 5; B.H. Shaw et al., *The Face of Postural Tachycardia Syndrome—Insights from a Large Cross-Sectional Online Community-based Survey*, 286 J. Internal Med. 438–448 (2019), filed as Ex. 39 (ECF No. 48-2) ("Shaw"). Based on a sample of nearly 5,000 survey participants reporting they had been diagnosed with POTS, 1,933 participants claimed their symptoms manifested within three months of a trigger, with six percent of that group identifying vaccination as the believed trigger. Shaw at 440. Shaw did not, however, determine the specific vaccines in question—and even noted its own methodologic weaknesses, such as the fairly significant fact that "we cannot verify that the diagnoses of POTS are correct in each case." *Id.* at 445.

The remainder of Dr. Miglis's first report was a detailed review of Petitioner's medical history. *See generally* Miglis First Rep. at 7–9. Overall, he emphasized that the record supported the POTS diagnosis, and that the three days from vaccination to onset were consistent with what relevant literature would consider medically acceptable. *Id.* at 10.

Second Report

Dr. Miglis's second report was filed around the time of Dr. Ahmed's (his co-expert) first report, and largely sought to respond to the contentions of Respondent's expert, Dr. Christopher Gibbons. First, Dr. Miglis questioned whether A.F.'s POTS could be deemed to have predated her receipt of the HPV vaccine, noting that she appeared overall quite active in that timeframe, and that her intermittent fainting episodes after blood draws (and while fasting, moreover) were more reflective of vasovagal syncope (which "commonly occurs in healthy young adults"). Miglis Second Rep. at 1. He also discounted Petitioner's Ehlers-Danlos syndrome as causal, characterizing it as potentially demonstrating that she was predisposed to POTS, but not undermining the likelihood that the HPV vaccine triggered it. *Id.*

Second, regarding whether POTS is generally associated with autoimmune conditions, Dr. Miglis discussed an item of literature criticized by Respondent's expert. Miglis Second Rep. at 2; S. Blitshteyn, *Autoimmune Markers and Autoimmune Disorders in Patients with Postural Tachycardia Syndrome (POTS)*, 24 Lupus 1364–1369, 1367 (2015), filed as Ex. 29 (ECF No. 47-2) ("Blitshteyn II"). Blitshteyn II involved blood testing for 100 POTS patients, in an attempt to identify certain kinds of known autoimmune markers, like a positive ANA.[15] Blitshteyn II at 1364–65. Approximately 25 percent of the tested group were positive for ANA (although titer levels were deemed primarily low), and other individuals were found to have distinguishable autoimmune disease-specific antibodies or had been diagnosed with a specific kind of autoimmune

[15] "ANA" refers to antinuclear antibodies. *Antinuclear Antibodies*, Dorland's Medical Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=56804 (last visited Oct. 11, 2022).

disorder. *Id.* at 1365. Dr. Miglis deemed these findings significant, despite Dr. Gibbons's argument that a positive ANA titer was not uncommon as a general matter (even in individuals not suffering from autoimmune conditions).

Dr. Miglis also re-emphasized the existence of a number of newer studies that associated POTS with the presence of specific kinds of anti-adrenergic receptor antibodies, observing that many had been undertaken since the HPV vaccine's administration became more prevalent (while admitting that these same studies "do not specify if Gardasil-vaccinated patients were included in their study population"). *Id;* Fedorowski at 4–5; Gunning at 2. A 2020 study, in fact, had provided support for the proposition that the levels of these autoantibodies in POTS patients correlated with the *severity* of orthostatic intolerance experienced. I. Kharraziha et al., *Serum Activity against G Protein-Coupled Receptors and Severity of Orthostatic Symptoms in Postural Orthostatic Tachycardia Syndrome*, 9 J. Am. Heart Assoc. 1–9, 8 (2020), filed as Ex. 74 (ECF No. 26-2) ("Kharraziha") (finding that the sera from 48 patients with POTS displayed more activation in four anti-adrenergic receptors compared to the sera from controls). But Kharraziha focused on receptor activity rather than autoantibody levels, assuming without confirmation that "the increased activity in the specific receptors is a consequence of autoimmune disease." Kharraziha at 8.

Dr. Miglis also noted that Petitioner had (nearly three years after onset) displayed slightly elevated titers of the purportedly-causal kinds of autoantibodies—and Dr. Miglis viewed the passage of time as supportive of the inference that her levels had likely *waned* since onset (although arguably testing results two-plus years after onset might not say anything at all about antibody levels in the past). Miglis Second Rep. at 3. Moreover, Dr. Miglis admitted not only that these autoantibodies could *not* be seen as biomarkers for POTS, but also that whether they were causative "or a bystander effect of dysimmunity" remained undetermined. *Id.*

Dr. Miglis took issue with some of the evidence that Respondent's expert marshalled against causation. Dr. Gibbons had noted, for example, that a large-scale report conducted by the European Medicines Agency (the "EMA")[16] had identified no POTS-HPV vaccine association. Miglis Second Rep. at 3; Pharmacovigilance Risk Assessment Committee, *Assessment Report: Review under Article 20 of Regulation (EC) No. 726/2004*, 1–40, 38–39 (2015), filed as Ex. A Tab 6 (ECF No. 18-7) (the "EMA Report"). But Dr. Miglis questioned whether the EMA Report had accurately identified instances of POTS based on the database codes it relied upon, and given how difficult POTS was generally to diagnose. Miglis Second Rep. at 3–4. And although he agreed that the counter-evidence he largely relied on came from case reports or case series articles, like Brinth and Kinoshita—a class of evidence "admittedly of weaker scientific merit"—they reflected the

[16] A decentralized agency of the European Union (EU), the European Medicines Agency (EMA) is responsible for the scientific evaluation, supervision, and safety monitoring of medicines within the EU. European Medicines Agency, *Who We Are*, https://www.ema.europa.eu/en/about-us/who-we-are (last visited Oct. 11, 2022).

observations of different nations, involving uncommon symptoms, and thus stood as "a signal of concern." *Id.* at 4.

By contrast, Dr. Miglis noted that a more recent, independent meta-analysis[17] (combining data from vaccine trials and clinical studies) had suggested that many HPV studies were "at a high risk of bias," due to comparison of vaccinated patients with controls who had also received adjuvant-containing vaccines, and that adverse occurrences that could be POTS-related were incompletely reported (but still more common in the context of receipt of the HPV vaccine). Miglis Second Rep. at 5; L. Jorgenson et al., *Benefits and Harms of the Human Papillomavirus (HPV) Vaccines: Systematic Review with Meta-Analysis of Trial Data from Clinical Study Reports*, 9 Systematic Reviews 1–23, (2020), filed as Ex. 75 (ECF No. 26-4) ("Jorgenson"). But Jorgenson's focus is far more on whether large-scale safety *testing* of the HPV vaccine is reliable, comparing overall claimed benefits for the vaccine (which it deemed uncertain) against a lack of emphasis on possible risks—and it referenced the same articles (Kinoshita and Brinth) as evidence of a POTS association, despite their lack of reliable findings on that front (as discussed above). Jorgenson at 2 nn. 27–28.

In similar fashion, Dr. Miglis attempted to vouch for other articles he offered in support of his contentions. For example, one article claimed to observe "clusters of symptoms" that could be POTS, but which could also simply reflect "availability bias," based on heightened awareness of the possibility of an HPV-associated injury. T. Ward et al., *A Cluster Analysis of Serious Adverse Event Reports after Human Papillomavirus in Danish Girls and Young Women*, 24 Euro Surveillance 1–10 (2019), filed as Ex. A-8 (ECF No. 18-9) ("Ward"). But Dr. Miglis maintained that this "increased awareness" might simply reflect better understanding of the diagnosis itself (and hence its existence, as opposed to a mistaken correlation). Miglis Second Rep. at 5.

Another study from Finland (which Dr. Gibbons had proposed showed that POTS diagnoses were already increasing *prior* to the widespread use of the HPV vaccine) did not, Dr. Miglis contended, involve the HPV vaccine, but relied (as Jorgenson observed) on inaccurate classification criteria to identify true instances of POTS, and ultimately could not reliably compare POTS incidence pre versus post-vaccination. *Id.* at 5–6; O. Skufca et al., *Incidence Rates of Guillain Barré (GBS), Chronic Fatigue/Systemic Exertion Intolerance Disease (CFS/SEID) and Postural Orthostatic Tachycardia Syndrome (POTS) prior to Introduction of Human Papillomavirus (HPV) Vaccination among Adolescent Girls in Finland*, 3 Papillomavirus Res. 91–96 (2017), filed as Ex. A Tab 9 (ECF No. 18-10) ("Skufca I").

[17] "Meta-Analysis" is defined as "a method for systematically combining pertinent qualitative and quantitative study data from several selected studies to develop a single conclusion that has greater statistical power." Himmelfarb Health Sciences Library, *Meta-Analysis*, https://himmelfarb.gwu.edu/tutorials/studydesign101/metaanalyses.cfm (last visited Oct. 11, 2022).

Dr. Miglis concluded by arguing that the position statement put out by the American Autonomic Society (the "AAS")—which expressly (and contrary to his fundamental opinion) *disavowed* an HPV vaccine-POTS association—could not be verified as reliable science, since it appeared more the opinion of certain "AAS senior members" than a replicable study with verifiable methodology, and also had been signed by biased individuals who has previously acted as witnesses for the Government in other litigation involving the HPV vaccine. Miglis Second Rep. at 6; A. Barboi et al., *Human Papillomavirus (HPV) Vaccine and Autonomic Disorders: A Position Statement from the American Autonomic Society*, 223 Autonomic Science: Basic and Clinical 102550 (2020), filed as Ex. A Tab 11 (ECF No. 18-12) (the "AAS Statement"). The AAS Statement—while expressly not a scientific study itself—reflects the views of 22 neurologists with expertise on autonomic conditions (including Dr. Gibbons himself), and highlights the fact that the overall benefits of the HPV vaccine outweigh the views expressed in articles like Brinth or Blitshteyn I, since they reveal "only weak temporal associations between events," and otherwise cannot be relied upon for causality given their "small sample sizes, inherent selection biases, and lack of control populations." AAS Statement at 3.

Third Report

The third report prepared by Dr. Miglis mostly attempted to analogize "autonomic complications" from COVID-19 infections to the circumstances at issue in this case. *See generally* Miglis Third Rep. at 1–4. Among the observed post-infectious symptoms and complications has been POTS —something Dr. Miglis deemed "not surprising," since POTS could also occur in the wake of other respiratory infections. *Id.* at 1–2. In fact, a case of POTS after receipt of the COVID-19 vaccine has been reported in one article. *Id.* at 2.[18] Other literature has suggested homology between the protein components of the COVID-19 coronavirus and human protein components, suggesting a "correlation of COVID-19 and autoimmunity." *Id.* Moreover, some recent studies demonstrated that individuals suffering from "long COVID" possessed the kind of anti-adrenergic autoantibodies that Dr. Miglis was contending herein could cause POTS. *Id.* at 3–4. Based on the foregoing, Dr. Miglis maintained that evidence of autoimmune processes driving POTS in the wake of a COVID-19 infection (or vaccination for that matter) had relevance to the contentions in this case as well. *Id.* at 4.

[18] Although Dr. Miglis has provided literature citations for these assertions, I do not reference them herein—for the simple, if obvious, reason that *the effects of the COVID-19 vaccine (or wild infection) are not in contention in this case whatsoever*. The general points Dr. Miglis sought herein to assert (about the role viruses can play in potentially causing POTS, and what that says about vaccines or an autoimmune-mediated form of POTS) can be understood and evaluated without consideration of the secondary support he offers for them, given the degree to which it strays far from the core questions presented by this claim.

B. *Petitioner's Expert — S. Sohail Ahmed, M.D.*

Dr. Ahmed, a clinical immunologist and rheumatologist with specific academic expertise in the study of vaccines and autoimmune conditions, prepared two additional reports for the Petitioner, offering an opinion proposing the biologic processes for how the HPV vaccine could produce the autoantibodies theorized in this case to cause POTS. Report, filed as Ex. 50 on November 28, 2020 (ECF No. 23-1) ("Ahmed First Rep."); Report, filed as Ex. 77 on March 17, 2021 (ECF No. 30-2) ("Ahmed Second Rep.").

Dr. Ahmed attended Johns Hopkins University for his undergraduate degree, and the University of Texas at Houston for his medical degree. *See* Curriculum Vitae, filed as Ex. 51 on November 28, 2020 (ECF No. 23-2) ("Ahmed CV") at 5; Ahmed First Rep. at 2. Dr. Ahmed has over 20 years of experience in academic and clinical research that facilitates translational approaches to drug development. Ahmed CV at 1; Ahmed First Rep. at 2. He currently serves as a medical and scientific consultant for pharmaceutical and vaccine-producing companies. Ahmed CV at 2; Ahmed First Rep. at 2–3. He has published several peer-reviewed articles on multiple topics including immune-meditated diseases, vaccine adjuvant safety, autoimmune diseases, immune mechanisms triggered by vaccination, autoantibodies linked to autoimmune diseases, and genetic susceptibility in patients developing autoimmune diseases. Ahmed CV at 6; Ahmed First Rep. at 3. He is licensed to practice medicine in Italy and Massachusetts and is board certified in rheumatology and internal medicine. Ahmed CV at 4–5; Ahmed First Rep. at 3.

First Report

Dr. Ahmed's first report highlighted his professional expertise and listed the materials he had considered in reaching the conclusions it contained, before going into the specific aspects of his opinion. Ahmed First Rep. at 1–4. He noted initially that the medical record confirmed that A.F. had not likely been experiencing POTS pre-vaccination. *Id.* at 5–7. He discounted the significance of her pre-vaccination syncopal events, observing that they had occurred in the context of blood draws, when she had fasted (presumably in preparation for the testing), and that otherwise she had not shown any clinical evidence of the diagnostic criteria for POTS. *Id.* at 7.

By contrast, the same record strongly established Petitioner's post-vaccination POTS diagnosis. Ahmed First Rep. at 8. In fact, Drs. Miglis and Gibbons so agreed. *Id.* Dr. Ahmed also (and relying on Dr. Gibbons's review of the medical history) proposed that Petitioner's POTS onset occurred within four days of vaccination. *Id.* He deemed such a timeframe consistent with how long an immune response leading into a pathologic autoimmune reaction would take post-vaccination, adding that corroboration for this putative process could be discerned from testing evidence of an elevated white blood cell count in early January 2018—confirming the presence of systemic inflammation. *Id.*

Dr. Ahmed then reached the heart of his report: that the HPV vaccine can cause POTS (as well as other immune-mediated diseases). Ahmed First Rep. at 9–12. But he heavily relied on arguments contained in Dr. Miglis's first report, as well as the literature cited therein, for this opinion. Thus, a whole page of Dr. Ahmed's report was devoted to a brief recapitulation of the findings in articles like Kinoshita, Brinth, and Blitsheyn I.[19] *See, e.g.*, Ahmed First Rep. at 9. He did the same in offering a potential biologic explanation for how the HPV vaccine would cause autoimmunity leading to POTS. *Id.* at 10; *See e.g.*, Blitshteyn I at 138; Li II at 8.

Dr. Ahmed proposed a biologic mechanism he deemed to be likely implicated in the pathogenic course of post-HPV vaccine POTS. Ahmed First Rep. at 10–11. Molecular mimicry, he explained, could occur when antigens in an infectious agent or vaccine could display "self-like peptides" (amino acid sequences that constitute the building blocks of proteins), generating antibodies that in turn would (due to antigenic similarity) attack not just the presenting antigen but the self-structure as well—an autoimmune cross-reaction. *Id.* at 11. Other common autoimmune diseases, like Guillain-Barré syndrome ("GBS") or lupus, were thought to be mediated by molecular mimicry due to the influenza vaccine—and the same was possible with POTS.

For direct support regarding the latter aspect of this contention, Dr. Ahmed offered a 2018 paper. Y. Segal & Y. Shoenfeld, *Vaccine-induced Autoimmunity: The Role of Molecular Mimicry and Immune Cross-reaction*, 15 Cellular & Molecular Immunology, 586–594 (2018), filed as Ex. 69 (ECF No. 25-3) ("Segal"). Dr. Ahmed maintained that Segal noted a "vast peptide overlap" between HPV amino acid sequences and "the human proteome," thus allowing for at least a speculative possibility of molecular mimicry. Ahmed First Rep. at 11. More specifically, Segal had itself cited a study (Li I) in which the sera of 14 POTS patients were shown to possess the anti-adrenergic antibodies that Dr. Miglis had proposed could be causal—and molecular mimicry, Dr. Ahmed argued, explained how they would come into existence. *See e.g.*, Segal at 591; Li I at 2.

A connection between the HPV vaccine and possible autoantibodies mediating POTS had also been explored in a different article, although it focused more on an autoantibody theorized to interact with cardiac myosin (a putative target for an autoimmune attack that could result in

[19] Dr. Ahmed also referenced a review paper based on data derived from the Vaccine Adverse Event Reporting System ("VAERS"). Ahmed First Rep. at 8–9; Miglis Rep. at 6 (citation omitted). VAERS is a national warning system designed to detect safety problems in U.S.-licensed vaccines. *See generally Carda v. Sec'y of Health & Hum. Servs.*, No. 14-191V, 2017 WL 6887368, at *6 (Fed. Cl. Spec. Mstr. Nov. 16, 2017). I provide no detailed consideration of this item, however—for the simple reason that (as has been often observed in prior Program cases) *VAERS data is unreliable proof of causation entitled to little probative weight. See Thompkins v. Sec'y of Health & Hum. Servs.*, No. 10-261V, 2013 WL 3498652 at *9 n.25 (Fed. Cl. Spec. Mstr. June 21, 2013). The fact that an individual reports a particular reaction post-vaccination does not make it more likely that the reaction was vaccine-caused—and VAERS diagnoses cannot necessarily even be confirmed as accurate in many cases. (Of course, I would reach the same conclusion about a study that attempted to undermine a vaccine-injury association by assembling VAERS data to show individuals were not routinely claiming the injury as a post-vaccination adverse event).

arrhythmias). Ahmed First Rep. at 11, S. Dahan et al., *Postural Orthostatic Tachycardia Syndrome (POTS)—A Novel Member of the Autoimmune Family*, 25 Lupus 339–342 (2016), filed as Ex. 70 (ECF No. 25-4) ("Dahan"). Dahan claimed to have observed homology between sequences in one of the HPV vaccine antigens and relevant human antigens associated with arrhythmias, allowing in turn for the possibility that the vaccine's spurring of an immune response involving the production of antibodies could spark the necessary cross-reaction to cause POTS. Dahan at 341. Thus, Dr. Ahmed was able to conclude that the HPV vaccine could more likely than not cause POTS. However, Dahan is (by its own title) an editorial, rather than a study, relying on other publications for the proposed amino acid homologies, and largely assuming (without a showing) that the sequential identifies result in cross-reactive pathogenicity.

Second Report

Dr. Ahmed's second report was prepared almost a month after Dr. Gibbons's responsive report, and consisted of a litany of rejoinders to points made by Dr. Gibbons. Dr. Ahmed initially offered some general contentions about the difficulty in identifying a post-vaccination "epidemiological signal," especially since vaccines are intentionally designed to be as safe as possible. Ahmed Second Rep. at 1. But evidence of "signals" supporting causation still exists, proving at least causality for "certain genetically predisposed subjects in the population." *Id.* at 2. Only if a study was especially large could such signals ever be reliably detected; thus, GBS (a rare disease generally) was causally associated with the flu vaccine as a result of "a mass immunization campaign" in 1976 (allowing for subsequent epidemiologic data to be gathered that would otherwise not have been available). *Id.*

Regarding the mechanism for how the HPV vaccine could cause POTS, Dr. Ahmed defended the legitimacy of Blitshteyn I's endorsement. Even if the article did not provide specific scientific support evidencing the mechanism in the context of POTS, its author is "an autonomic specialist," and it references case report examples of individuals whose POTS was argued to have been vaccine-caused, based on clinical evaluation of alternative explanations. Ahmed Second Rep. at 3; Blitshteyn I at 138. The same author noted in a different article (Blitshteyn II) that there was an association between POTS and the existence of ANA, a likely autoimmunity biomarker. Blitshteyn II at 1367.

Moreover, other literature corroborated a POTS-autoimmunity link. Ahmed Second Report at 2–3; Dahan at 3 (proposing immune cross-reaction causing arrhythmia, based on HPV peptide sequences having some kind of homologous similarity with human proteins). Some articles also establish that POTS can occur after viral infections (including COVID-19 infections), further underscoring the likelihood of an autoimmune basis for the condition. Ahmed Second Rep. at 3; M. Thieben et al., *Postural Orthostatic Tachycardia Syndrome: The Mayo Clinic Experience*, 82 Mayo Clin. Proc. 308–313, 308, (2007), filed as Ex. 79 (ECF No. 30-4) ("Thieben") (suggesting

that there is a neuropathic basis for roughly half of the cases of POTS, and of those cases, a substantial percentage may be autoimmune). All of the above provided support for the hypothesis that molecular mimicry leading to a cross-reaction might explain how a vaccine (like a virus) could result in POTS. Dr. Ahmed also argued that the animal study from Li II was reliable, and provided substantiation for an association between anti-adrenergic autoantibodies and POTS. Ahmed Second Rep. at 4–5; Li II at 8.

In addition, Dr. Ahmed attempted to rebut Dr. Gibbons's contention that the testing performed on Petitioner in August 2020 was unreliable or unsupportive of her argument that she did likely possess the autoantibodies alleged to be causal of POTS. First, he cited an additional item of literature from Japan, in which 55 young girls who had received the HPV vaccine were tested (using the same European testing company utilized for Petitioner (*see* Ex. 48)) for the relevant autoantibodies (including the "anti-ETAR" autoantibodies that Dr. Gibbons had identified as likely irrelevant, but which Petitioner tested for in 2020 as "at risk"). Ahmed Second Rep. at 5; A. Hineno et al., *Autoantibodies Against Autonomic Nerve Receptors in Adolescent Japanese Girls after Immunization with Human Papillomavirus Vaccine*, 2 Annals of Arthritis and Clinical Rheumatology 1–6 (2019), filed as Ex. 82 (ECF No. 30-7) ("Hineno"). Hineno found that the tested subjects (all of whom had reported a variety of symptoms after receipt of an HPV vaccine) possessed higher levels of the relevant autoantibodies than controls, concluding that autoantibodies were likely associated with "orthostatic dysregulation." Hineno at 4. The capacity of these autoantibodies to cause POTS was confirmed by articles like Thieben, which showed that viral infection could cause their presence as well. Thieben at 310. Like other articles attempting to connect these autoantibodies to POTS, however, Hineno allowed that "the exact pathogenesis of orthostatic deregulation . . . after HPV vaccination remains unclear," and also that (a) POTS can develop in unvaccinated individuals, and (b) some of the Hineno control subjects also possessed the purportedly-causal autoantibodies without developing POTS. Hineno at 2, 4. In addition, Hineno possesses the same self-selection bias limitations as articles like Kinoshita, since the tested subjects had all self-reported post-vaccination symptoms after vaccination. *Id.* at 2.

Second, Dr. Ahmed vouched for the reliability of the specific testing that Petitioner received in 2020 (and which studies like Hineno relied upon). He disputed Dr. Gibbons's argument that the testing only identified non-specific autoantibodies not shown to be relevant to a particular disease, noting that other kinds of comparable non-specific testing (such as testing for rheumatoid factor) was available in the U.S. Ahmed Second Rep. at 6. And he maintained that the autoantibodies tested by the European testing center had in fact been demonstrated as relevant to POTS. *Id.* The location of the testing center did not bear on whether the results were reliable or relevant.

C. *Respondent's Expert – Christopher Gibbons, M.D.*

Dr. Gibbons, a neurologist with expertise in autonomic-oriented conditions such as POTS, served as Respondent's sole expert, preparing three reports. Report, filed as Ex. A on June 18, 2020 (ECF No. 18-1) ("Gibbons First Rep."); Report, filed as Ex. C on March 2, 2021 (ECF No. 29-1) ("Gibbons Second Rep."); Report, filed as Ex. D on October 27, 2021 (ECF No. 36-1) ("Gibbons Third Rep.").

Dr. Gibbons attended Dartmouth College for his undergraduate degree, and Albert Einstein College of Medicine for his medical degree. *See* Curriculum Vitae, filed as Ex. B on June 18, 2020 (ECF No. 18-15) ("Gibbons CV") at 1–2; Gibbons First Rep. at 1. Thereafter, Dr. Gibbons completed a neurology residency at Johns Hopkins Hospital in Baltimore, Maryland, and a fellowship in clinical neurophysiology (with a subspecialty in autonomic disorders) from Beth Israel Deaconess Medical Center in Boston, Massachusetts. Gibbons CV at 1. He is an Associate Professor of Neurology at Harvard Medical School and is a board-certified neurologist, with subspecialty qualification in Clinical Neurophysiology. Gibbons CV at 1; Gibbons First Rep. at 1. Currently, Dr. Gibbons serves as Co-Director of the Autonomic Disorders Clinic at Beth Israel where he teaches resident and autonomic disorders fellows about autonomic testing and the treatment of autonomic disorders. *Id*. In addition to the above, Dr. Gibbons has also served as the President of the American Autonomic Society and Chair of the Autonomic Section of the American Academy of Neurology. Gibbons CV at 3; Gibbons First Rep. at 1.

Over the course of his career, Dr. Gibbons has repeatedly in his clinical practice evaluated and treated patients with POTS and has tested approximately 100 POTS patients per year in the autonomic laboratory. Gibbons First Rep. at 1. In addition to his clinical work, Dr. Gibbons has given numerous national and international lectures on the topic of autonomic disorders and POTS, and has published over 100 research articles, chapters, and books on the subject matter. *Id*. Dr. Gibbons does not have specific expertise in immunologic issues.

First Report

Dr. Gibbons provided his own overview of A.F.'s medical history as revealed by the filed records. Gibbons First Rep. at 1–2. He specifically noted that there was in the record some reference to pre-vaccination syncopal events, although he acknowledged it was vague in nature. *Id.* at 2–3. He then provided a definition of POTS largely consistent with what Dr. Miglis had proposed (including its characteristics and diagnostic factors)—although he gave more emphasis to the wide variety of explanations for it (for example, astronauts often experienced POTS after space voyages due to deconditioning they experienced "in the absence of gravity"). *Id.* at 2; R. Freeman et al., *Consensus Statement on the Definition of Orthostatic Hypotension, Neurally Mediated Syncope, and the Postural Tachycardia Syndrome,* 161 Autonomic Neuroscience: Basic

and Clinical 46 (2011), filed as Ex. A Tab 1 (ECF No. 18-2) ("Freeman"), at 48 (deeming POTS's etiology "likely to be heterogeneous," and "associated with deconditioning, recent viral illness, chronic fatigue syndrome and a limited or restricted autonomic neuropathy"). POTS could also manifest in the presence of other disorders, like thyroid issues, anxiety, dehydration, or as a side-effect of certain medications. *Id.*[20]

Dr. Gibbons accepted Petitioner's POTS diagnosis. Gibbons First Rep. at 3. But he denied any causal relationship between POTS and the HPV vaccine. First, he took issue with the extent to which POTS could be considered reliably associated with autoimmunity. *Id.* at 3–4. He noted that one article relied upon by Dr. Miglis to establish a general POTS/autoimmunity connection, Blitshteyn II, emphasized the degree to which a large percentage of POTS patients had a specific ANA titer—a measure Dr. Gibbons denied was clinically significant, especially since many individuals also possessed that titer level. *Id.* at 3; Blitshteyn II at 1367.

More specifically, Dr. Gibbons questioned the probative value of the articles referenced by Dr. Miglis for the proposition that POTS patients often tested positive for certain kinds of anti-adrenergic autoantibodies believed to potentially be associated with some instances of POTS. He emphasized the small sample sizes at issue in such articles, and lack of "validated" testing methodologies to confirm the presence of such autoantibodies in the first place. Gibbons First Rep. at 4. He further denied the existence of "reliable or persuasive evidence that these antibodies are pathogenic," adding that the patient sample groups in some instances were not even comparable to Petitioner—since they involved patients far older, and who likely had not received an HPV vaccine pre-testing (given that the studied samples were pre-2013, when the HPV vaccine became more prevalent). *Id;* Fedorowski at 1212. The relevant autoantibodies were also detected in other non-comparable patients with different diseases (dementia or ocular disease, for example), further diminishing the likelihood that they were as specific to POTS as alleged. A. Miller & T. Doherty, *Hop to It: The First Animal Model of Autoimmune Postural Orthostatic Tachycardia Syndrome*, 8 J. Am. Heart Assoc. 1–3, 2 (2019), filed as Ex. A Tab 5 (ECF No. 18-6) ("Miller") at 3 (editorial commenting on Li II animal model, and noting questions about "how well this rabbit model of POTS represents the heterogeneous patient population and whether it will contribute to further advancements toward novel therapeutics for POTS"). Dr. Gibbons echoed Miller's concern that "it is unclear whether the presence of adrenergic autoantibodies in participants with POTS is a bystander effect of the primary disease process or whether they are centrally pathogenic"). Miller at 2.

[20] Dr. Gibbons also discussed Ehlers Danlos syndrome, explaining that it too could often result in POTS as a secondary symptom—and might even explain Petitioner's POTS. Gibbons First Rep. at 2–3. Although a credible case could be made based on the evidence filed herein that A.F.'s POTS was attributable to her diagnosed Ehlers Danlos syndrome, I am resolving the case based on the more fundamental finding that the HPV vaccine does not likely cause POTS.

The case report series articles Dr. Miglis cited as connecting POTS to the HPV vaccine were in Dr. Gibbons's view equally deficient. As discussed above, Dr. Gibbons emphasized that the sample groups in articles referenced were often subject to selection/referral bias, since only patients who sought care for suspected vaccine reactions were considered, and without unvaccinated controls. Gibbons First Rep. at 4. Another article found that reported increases of post-HPV vaccination POTS "were likely related to increased attention on the diagnosis of POTS in the setting of medical reports," rather than a causal relationship. Gibbons First Rep. at 5; Ward at 8.

Dr. Gibbons also cited two large-scale observational studies that he maintained undermined any POTS/HPV vaccine association. One was prepared by the EMA. Gibbons First Rep. at 4; EMA Report at 38 (concluding that "[o]verall, available data do not provide support for a causal relationship between HPV vaccines and POTS," and criticizing Brinth for conflating POTS with chronic fatigue syndrome). Another, from Finland, considered the incidence of POTS, among other illnesses, after receipt of the HPV vaccine over a ten-year period (2002-12), with no evidence that POTS was increasing after the vaccine was becoming widespread in use (while confirming Ward's finding that mere awareness of the diagnosis of POTS was producing speculation that post-vaccination causation was a possibility). Skufca I at 94–95. Indeed, at least one article observed a *decrease* in incidence of POTS after introduction of the vaccine (compared to years when it was not utilized). J. Skufca et al., *The Association of Adverse Events with Bivalent Human Papillomavirus Vaccination: A Nationwide Register-based Cohort Study in Finland*, 36 Vaccine 5926–5933 (2018), filed as Ex. A Tab 10 (ECF No. 18-11) ("Skufca II").

Ultimately, the most reliable scientific authorities on the topic (in Dr. Gibbons's estimation) had expressly discounted any reliable causal relationship between POTS and receipt of the HPV vaccine. Gibbons First Rep. at 5; AAS Statement at 3. Dr. Gibbons was a co-signer of the AAS Statement, which maintained that "[l]arge population studies and exposure of over 270 million people to the HPV vaccine have not resulted in an identifiable pattern of adverse events, and no evidence of an increase in dysautonomia or POTS with use of the vaccine." AAS Statement at 3.

Second Report

Dr. Gibbons's second report endeavored to succinctly respond to objections leveled against the contents of his initial opinion by Drs. Miglis and Ahmed. Dr. Miglis, he maintained, placed too much emphasis on the mere fact that there was a temporal association between the HPV vaccine and Petitioner's POTS—an insufficient basis for a finding of causality. Gibbons Second Rep. at 2. Petitioner's possession of the purportedly-causal anti-adrenergic autoantibodies was in

fact not confirmed on testing from August 2020 (two and one-half years after vaccination),[21] and otherwise the results were not reliable. Ex. 48 at 1. The testing at issue, he noted, is not available within the U.S. Moreover, the two types of autoantibody that the testing suggested were even slightly elevated, such as "anti ETAR" autoantibodies, had not been shown under the Petitioner's causation theory to be possibly pathogenic in the context of POTS. *Id.*

Dr. Gibbons also reiterated his prior argument questioning whether the purportedly pathogenic autoantibodies identified in Dr. Miglis's theory could actually initiate POTS. These kinds of autoantibodies "are not specific for any disease," and have been identified in association with a broad number of other conditions. Gibbons Second Rep. at 3; S. Vernino & L. Stiles, *Autoimmunity in Postural Orthostatic Tachycardia Syndrome: Current Understanding*, 215 Autonomic Neuroscience: Basic and Clinical 78 (2018), filed as Ex. C Tab 1 (ECF No. 29-2) ("Vernino"). Although Vernino emphasized (consistent with other general articles) that "POTS likely has a heterogeneous pathophysiology," it discussed the existing state of scientific understanding of potential autoimmune factors in some cases of POTS—and specifically the GPCR/anti-adrenergic autoantibodies proposed as causal in this case. Vernino at 80. But the article notes that these autoantibodies "are not novel," and have been observed in connection with general cardiovascular disorders, thyroid issues, and specific known autoimmune diseases. *Id.* Ultimately, Vernino proposed that because these autoantibodies are seen in so many diverse illnesses or conditions, "they may represent an immune response to tissue injury or some sort of physiological regulatory response to cardiac stress." *Id.* This is not consistent with this class of autoantibodies being initially *causal* of POTS.

In addition, Dr. Gibbons made several observations about weaknesses in various items of literature offered to support Petitioner' causation theory. Fedorowski, for example, likely had a sample of patients not comparable to A.F. in age. Gibbons Second Rep. at 3; Fedorowski at 2. Gunning, by contrast, likely included a population that had *not* even received the vaccine, based upon their age at the time of the study. Gibbons Second Rep. a 3; Gunning at 2. And Dr. Gibbons rejected Dr. Miglis's argument that the AAS Statement was unreliable because it did not include all AAS members as signatories, noting that dissenting members could have made their views known had they objected to its contents.

Dr. Gibbons also commented on Dr. Ahmed's attacks.[22] He did not find that studies involving very small patient samples, like Kinoshita (44 patients) and Blitsheyn I (six patients),

[21] Dr. Gibbons also expressed skepticism toward Dr. Miglis's argument that "maybe the antibody titers have declined" for Petitioner in the time since vaccination more than two years before (which might explain why certain relevant autoantibodies were undetected, or only deemed to be at levels considered "at risk"). Gibbons Second Rep. at 3.

[22] Dr. Gibbons initially reiterated the view (mentioned in footnote 11 above) that Shaw is nothing more than an online survey that lacks core methodologic reliability. Gibbons Second Rep. at 1. I do not expand on this attack, however, since I consider the fundamental deficiency of Shaw's methodology deprives it significant scientific reliability, and hence it merits little weight in my analysis.

that purported to identify "very modest temporal associations" between the HPV vaccine and POTS, were especially probative of a causal association. Gibbons Second Rep. at 2. He also noted a variety of omissions in Dr. Ahmed's logical causation chain. Comparisons to GBS, for example, were unavailing, since it is a "well characterized autoimmune disorder" with reliably-researched characteristics that bear on vaccine causation. *Id.* POTS, by contrast, "is a poorly defined series of symptoms . . . that can be due to any number of" causes, "and has only been hypothesized to be due to autoimmune disease." *Id.* And the very limited amount of case report evidence, in comparison to the number of vaccine doses given, suggested a lack of probative evidence connecting the two. *Id.*

Another challenge Dr. Gibbons raised to Dr. Ahmed's opinion was the proposition that the HPV vaccine could mediate POTS via molecular mimicry. Dr. Ahmed relied on Blitshteyn I for this aspect of his theory—even though the article *itself* was (a) penned by "a general neurologist with no training in immunology," and (b) contained no independent evidence that POTS could in fact be mediated through this specific autoimmune mechanism. Gibbons Second Rep. at 2; Blitshteyn I at 138. Dr. Ahmed also cited Li II's animal model, but the heart rate increase that had been observed was only a ten percent increase—not sufficient to meet a POTS diagnosis. Gibbons Second Rep. at 2. In addition, the tested rabbits in Li II are quadrupeds that do not typically face the orthostatic stress of standing upright, and hence the tested heartrate changes observed in Li II "are of unclear relevance to the human condition." Gibbons Second Rep. at 2.

Third Report

Dr. Gibbons's final report responded only to the third, short report offered by Dr. Miglis (which as noted above sought solely to analogize some recent studies about COVID-19 and its association with POTS to the present case). He characterized the general state of scientific study of COVID-19 and its secondary symptomatic features as "dynamic and unsettled," maintaining the view that not enough was known about how the coronavirus can impact the nervous system generally to draw the conclusions Dr. Miglis proposed. Gibbons Third Rep. at 1. He also noted that there were competing mechanistic theories for how COVID-19 might produce neurologic manifestations, with molecular mimicry serving as only one possibility that had yet to be fully embraced or confirmed. *Id.* Dr. Gibbons also noted that one of the articles referenced by Dr. Miglis as evidence of a COVID-19 relationship with the relevant autoantibodies was too limited in sample scope (an "N of 1" trial, rather than a study with many sampled subjects), and also involved evidence of the relevant autoantibodies long predating the COVID-19 diagnosis. *Id.* He thus concluded that this evidence, while interesting, could not be persuasively marshaled to support the causation theory in this case.

III. Procedural History

As noted above, the case was initiated in March 2019. In lieu of a Rule 4(c) Report, Respondent filed a status report stating their initial reaction to the claim. ECF No. 15. Following the filing of pertinent medical records and an affidavit, Petitioner offered Dr. Miglis's first expert report in February 2020. ECF No. 16. Thereafter Respondent filed his first expert report from Dr. Gibbons in June 2020, and Petitioner filed an expert report from Dr. Ahmed in November 2020. ECF Nos. 18, 23. Respondent's expert filed two supplemental reports, and Petitioner's expert Dr. Ahmed filed an additional supplemental report with Dr. Miglis filing two supplemental reports. ECF Nos. 26, 29, 30, 34, 36. The parties fully briefed the matter by April 2022, and it is now ripe for resolution.

IV. Parties' Arguments

Petitioner

Petitioner argues that she has established causation under the three-prong test set by the Federal Circuit in *Althen v. Sec'y of Health and Hum. Servs.,* 418 F.3d 1274, 1278 (Fed. Cir. 2005). Mot. at 1. As Petitioner's experts emphasized, there is a growing consensus within the medical community that POTS can be immune-mediated for genetically predisposed individuals. Mot. at 2; Reply at 2, 5. Many studies have identified GPCR/anti-adrenergic autoantibodies believed to play a role in the pathogenesis of the immune-mediated form of POTS. Mot. at 2; Reply at 2, 4. Molecular mimicry is a biologically plausible mechanism linking the HPV vaccine to POTS (just as it has applicability in the context of other known autoimmune disease processes). Reply at 2–3. In particular, the HPV vaccine could initiate "an immune response that triggers an autoimmune response that progresses to an autoimmune condition." Reply at 4, 6; Ahmed First Rep. at 8, 71.

To support her causation theory, Petitioner highlighted some of the more recently-published articles or studies her experts had discussed. Reply at 2, 4. Federowski, for example, indicated autoantibodies play a role in the pathophysiology of POTS, and Gunning supported the theory that POTS could actually be an autoimmune disorder. Reply at 5; Federowski at 1214–15; Gunning at 9. Moreover, an animal study, Li II, had more directly linked adrenergic autoantibodies and POTS. Reply at 6; Li II at 8. And Hineno suggested some symptoms following vaccination might be attributed to an abnormal autoimmune response. Reply at 5; Hineno at 5. Respondent, by contrast, relied heavily on less-contemporaneous articles. Reply at 7. Thus, the many new scientific developments (including studies about COVID-19's link to POTS) provided the kind of reliable evidence lacking from prior cases. Reply at 4, 7–9.

Petitioner also argued that the record supported the conclusion that the HPV vaccine likely had caused her POTS. She had never experienced the symptoms that were later diagnosed as POTS until after she received the vaccine, and several of her treaters deemed an association credible.

Mot. at 2; Reply at 2, 9. And her four-day post-vaccination onset fell within a medically acceptable timeframe "for a vaccine to generate an immune response and then lead to an autoimmune response." Mot. at 3; Reply at 1, 6; Ahmed First Rep. at 8.

Respondent

Respondent did not dispute Petitioner's POTS diagnosis, but argued that she had failed to satisfy the three *Althen* prongs necessary to establish entitlement. Opp. at 1. Respondent denied the existence of reliable evidence linking the HPV vaccine to POTS, and emphasized that no claim alleging such an association has been successful in the Vaccine Program (at least to date). *Id*. at 2. Respondent in particular highlighted Petitioner's failure to address the lack of evidence suggesting POTS is an immune mediated disease, even in part. *Id*. at 12, 17.

Regarding some of the specific components of Petitioner's causation theory, Respondent disputed that the articles suggesting many POTS patients possess certain autoantibodies were compelling, noting that there is no "approved and validated test for these antibodies," let alone reliable proof that they are in fact pathogenic. Opp. at 13–14, 17. Respondent also maintained that Dr. Miglis had assumed POTS patients displaying these autoantibodies had received an HPV vaccine, even though neither Fedorowski nor Gunning established that to be the case. *Id*. at 15. Indeed, given the ages of the sample populations in such articles, it was unlikely that the participants had received the HPV vaccine. Opp. at 15. In addition, Respondent maintains that Blitshteyn II only showed the same rates of autoimmunity that would be expected in the general population. Opp. at 13. And it was "premature" to offer studies relating to COVID-19's alleged association with POTS, especially given their lack of direct relevance to the HPV vaccine. Opp. at 17; Ex. 85 at 2–4.

In counter to Petitioner's literature, Respondent invoked Vernino, arguing that it raised compelling questions about autoimmune causes for POTS. Opp. at 13; Vernino at 79–80. Vernino also found that no antibody is specifically understood to be likely causative of POTS, and thus there was "insufficient proof of an autoimmune cause for POTS based on the current research." Opp. at 14–15. And the autoantibodies proposed to be mediating post-HPV vaccine POTS are frequently found in healthy individuals, "have not been demonstrated as antigenic in any context," and have not even been shown to be pathogenic in any regard, despite being "described in many disorders". Opp. at 14. Respondent also maintained that there exist some large-scale epidemiologic evidence undermining the contention that the HPV vaccine can cause POTS. *Id.* at 15–16; Skufca II at 1.

Otherwise, Respondent argued, Petitioner could only demonstrate a temporal association between the vaccination at issue and Petitioner's POTS. Opp. at 18–19. She failed to offer medically-acceptable proof of a "metric establishing a timeframe that could be temporally appropriate." *Id*. at 20.

V. Applicable Legal Standards

A. *Petitioner's Overall Burden in Vaccine Program Cases*

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury"—i.e., an injury falling within the Vaccine Injury Table—corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).[23] In this case, Petitioner does not assert a Table claim, nor does there exist such a claim for POTS (or autonomic disfunction generally) as the injury.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Hum. Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Hum. Servs.*, 165 F.3d 1344, 1352–53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Hum. Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a Non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen,* 418 F.3d at 1278: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and

[23] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Hum. Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Hum. Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd* 104 F. Appx. 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Hum. Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

injury." Each *Althen* prong requires a different showing and is discussed in turn along with the parties' arguments and my findings.

Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355–56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

However, the Federal Circuit has *repeatedly* stated that the first prong requires a preponderant evidentiary showing. *See Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351, 1360 (Fed. Cir. 2019) ("[w]e have consistently rejected theories that the vaccine only "likely caused" the injury and reiterated that a "plausible" or "possible" causal theory does not satisfy the standard"); *see also Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Broekelschen v. Sec'y of Health & Hum. Servs*., 618 F.3d 1339, 1350 (Fed. Cir. 2010). This is consistent with the petitioner's ultimate burden to establish his overall entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Hum. Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted). If a claimant must *overall* meet the preponderance standard, it is logical that they be required also to meet each individual prong with the same degree of evidentiary showing (even if the *type* of evidence offered for each is different).

Petitioners may offer a variety of individual items of evidence in support of the first *Althen* prong, and are not obligated to resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378–79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325–26). No one "type" of evidence is required. Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu,* 569 F.3d at 1380. Nevertheless, even though "scientific certainty" is not required to prevail, the individual items of proof offered for the "can cause" prong must *each* reflect or arise from "reputable" or "sound and reliable" medical science. *Boatmon,* 941 F.3d at 1359–60.

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Hum. Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d

at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Hum. Servs*., 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record—including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Hum. Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Hum. Servs.*, No. 06–522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356–57 (2011), *aff'd without opinion*, 475 F. App'x. 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Hum. Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Hum. Servs.*, No. 11–355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. *Law Governing Analysis of Fact Evidence*

The process for making determinations in Vaccine Program cases regarding factual issues

begins with consideration of the medical records. Section 11(c)(2). The special master is required to consider "all [ ] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Hum. Servs*., 3 F.3d 415, 417 (Fed. Cir. 1993) (determining that it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

As noted by the Federal Circuit, "[m]edical records, in general, warrant consideration as trustworthy evidence." *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Hum. Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"), *aff'd*, *Rickett v. Sec'y of Health & Hum. Servs*., 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). A series of linked propositions explains why such records deserve some weight: (i) sick people visit medical professionals; (ii) sick people attempt to honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Hum. Servs.*, No. 11–685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Hum. Servs.*, 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d at 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms").

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Hum. Servs*., No. 03–1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are often found to be deserving of greater evidentiary weight than oral testimony—especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; *see also Murphy v. Sec'y of Health & Hum. Servs*., 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, the Federal Circuit has also noted that there is no formal "presumption" that

records are accurate or superior on their face when compared to other forms of evidence. *Kirby v. Sec'y of Health & Hum. Servs.,* 997 F.3d 1378, 1383 (Fed. Cir. 2021). There are certainly situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Hum. Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility may be required when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Hum. Servs*., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Hum. Servs*., No. 90–2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *La Londe v. Sec'y of Health & Hum. Servs*., 110 Fed. Cl. 184, 203–04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. *Analysis of Expert Testimony*

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Hum. Servs*., 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594–96 (1993). *See Cedillo v. Sec'y of Health & Hum. Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). Under *Daubert*, the factors for analyzing the reliability of testimony are:

> (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether

> there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.

Terran, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592–95).

However, in the Vaccine Program the *Daubert* factors play a slightly different role than they do when applied in other federal judicial settings—e.g., the district courts. Typically, *Daubert* factors are employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable or could confuse a jury. By contrast, in Vaccine Program cases these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Hum. Servs*., 94 Fed. Cl. 53, 66–67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness and reliability of expert testimony has routinely been upheld. *See, e.g.*, *Snyder*, 88 Fed. Cl. at 742–45. In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)); *see also Isaac v. Sec'y of Health & Hum. Servs*., No. 08–601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 F. App'x. 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Hum. Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

D. *Consideration of Medical Literature*

Both parties filed numerous items of medical and scientific literature in this case, but not

every filed item factors into the outcome of this Decision. While I have reviewed all the medical literature submitted in this case, I discuss only those articles that are most relevant to my determination and/or are central to Petitioner's case—just as I have not exhaustively discussed every individual medical record filed. *Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted); *see also Paterek v. Sec'y of Health & Hum. Servs.,* 527 F. Appx. 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered").

E. *Disposition of Case Without Hearing*

I am resolving Petitioner's claim on the filed record. The Vaccine Act and Rules not only contemplate but encourage special masters to decide petitions on the papers where (in the exercise of their discretion) they conclude that doing so will properly and fairly resolve the case. Section 12(d)(2)(D); Vaccine Rule 8(d). The decision to rule on the record in lieu of hearing has been affirmed on appeal. *Kreizenbeck v. Sec'y of Health & Hum. Servs*., 945 F.3d 1362, 1366 (Fed. Cir. 2020); *see also Hooker v. Sec'y of Health & Hum. Servs*., No. 02-472V, 2016 WL 3456435, at *21 n.19 (Fed. Cl. Spec. Mstr. May 19, 2016) (citing numerous cases where special masters decided case on the papers in lieu of hearing and that decision was upheld). I am simply not required to hold a hearing in every matter, no matter the preferences of the parties. *Hovey v. Sec'y of Health & Hum. Servs*., 38 Fed. Cl. 397, 402–03 (1997) (determining that special master acted within his discretion in denying evidentiary hearing); *Burns*, 3 F.3d at 417; *Murphy v. Sec'y of Health & Hum. Servs.*, No. 90-882V, 1991 WL 71500, at *2 (Fed. Cl. Spec. Mstr. Apr. 19, 1991).

ANALYSIS

I. POTS Has Not Previously Been Found to be Caused by the HPV Vaccine

The parties agree A.F. was appropriately diagnosed with POTS—leaving primarily the question of whether POTS *can* be caused by the HPV vaccine.

There are *no* persuasive reasoned Program decisions finding that the HPV vaccine can interfere with any aspect of the nervous system sufficiently to cause *any* form of orthostatic intolerance—whether manifesting as vasovagal syncope, POTS, or some other comparable autonomic dysfunction. *See, e.g., E.S. v. Sec'y of Health & Hum. Servs.*, No. 17-480V, 2020 WL 9076620, at *42 (Fed. Cl. Spec. Mstr. Nov. 13, 2020), *mot. for review den'd*, 154 Fed. Cl. 149 (2021) ("[a]lthough I am considering a large number of alleged injuries [specifically, headaches, chronic fatigue syndrome, POTS, and small fiber neuropathy] . . . I universally find that Petitioner has not in *any* instance established [in this case] that the HPV or flu vaccines "can cause" the

relevant injury") (emphasis in original); *Balasco v. Sec'y of Health & Hum. Servs.*, No. 17-215V, 2020 WL 1240917, at *34 (Fed. Cl. Spec. Mstr. Feb. 14, 2020) (articulating that the special master "[did] not find preponderant evidence of a reliable medical theory causally connecting petitioner's HPV vaccinations to either POTS generally or her own fibromyalgia and/or vestibular migraines in particular"); *Johnson v. Sec'y of Health & Hum. Servs.,* No. 14-254V, 2018 WL 2051760, at *24 (Fed. Cl. Spec. Mstr. Mar. 23, 2018) (discussing how the petitioner failed to establish a reliable medical causation theory that the HPV vaccine established autonomic nervous system or orthostatic intolerance conditions); *Combs v. Sec'y of Health & Hum. Servs.*, No. 14-878V, 2018 WL 1581672, at * 1 (Fed. Cl. Spec. Mstr. Feb. 15, 2018) ("[p]etitioner's causation theory—that the HPV vaccine could damage the autonomic nervous system—was scientifically unreliable and unpersuasive . . . ."); *K.L. v. Sec'y of Health & Hum. Servs.,* No. 12-312V, 2017 WL 1713110, at *15 (Fed. Cl. Spec. Mstr. Mar. 17, 2017) (noting that respondent demonstrated more persuasively that there was "no link between a number of neurological events, including epilepsy, and receipt of the HPV vaccine"), *mot. for review den'd,* 134 Fed. Cl. 579 (2017); *L.A.M. v. Sec'y of Health & Human Servs*., No. 11–852V, 2017 WL 527576 (Fed. Cl. Spec. Mstr. Jan. 31, 2017) (concluding that the HPV vaccine not found to cause POTS); *Turkupolis v. Sec'y of Health & Human Servs.*, No. 10–351V, 2014 WL 2872215 (Fed. Cl. Spec. Mstr. May 30, 2014) (finding that the HPV vaccine not shown to cause neurocardiogenic syncope).

In almost all such prior cases, arguments akin to what are advanced herein were considered but rejected, often based on record evidence findings establishing the existence of POTS or some other form of orthostatic intolerance. *See, e.g., Balasco*, 2020 WL 1240917, at *13, 28, 34 (noting that petitioner (unlike in the present case) had a "positive tilt table test and tested positive for anti-alpha-1-adrenergic antibodies, anti-beta-2 adrenergic antibodies, and the anti-muscarinic cholinergic receptor 4 antibodies. . .", but unsuccessfully established that this raised the likelihood of autonomic dysautonomia, since there was not enough evidence to support the reliability or significance of the results); *McKown*, 2019 WL 4072113, at *50 (stating that molecular mimicry was not reliably invoked to explain vaccine association with syncopal symptoms); *see also Yalacki v. Sec'y of Health & Hum. Servs.*, No. 14-278V, 2019 WL 1061429, at *34 (Fed. Cl. Spec. Mstr. Jan. 31, 2019), *mot. for review den'd,* 146 Fed. Cl. 80 (2019) (commenting on petitioner's theory that the Hep B vaccine could trigger a pathogenic process resulting in an autoimmune attack leading to an injury, but finding that it was "not enough for a claimant to invoke the concept of molecular mimicry" as petitioner needed to "cite to evidence, circumstantial or otherwise, suggesting reason to find it plausible that the proposed autoimmune cross-reaction triggered by the relevant vaccine *does occur*") (emphasis in original).

In addition, these unsuccessful petitioners have commonly cited to many of the same items of literature offered herein, like Blitshteyn I and II, Brinth, and Kinoshita. But the articles have been criticized as unreliable or unpersuasive. *See, e.g., E.S.*, 2020 WL 9076620, at *45 (". . . evidence offered to suggest a case study-oriented association, like Kinoshita, is weak, dependent

on self-selected patient populations rather than scientifically-reliable studies."); *McKown*, 2019 WL 4072113, at *29, 51 (noting that although Brinth was used to suggest an association between the HPV vaccine and POTS, it revealed selection bias in the studied patients in its sample, and otherwise suffered from a lack of reliable scientific basis); *Johnson*, 2018 WL 2051760, at *17, 24 (articulating that Kinoshita and Brinth both involved self-selection and lacked scientifical reliability); *Combs*, 2018 WL 1581672, at *7 n.12, 18 (stating that the European medical institutions evaluated Kinoshita but determined that the figure supposedly showing a correlation between HPV vaccination and autonomic conditions was actually attributable to overreporting rather than a scientifically-based association). Literature filed by Respondent that provides an overview of these kinds of studies confirms their unreliable and unpersuasive character. B. Butts et al., *Human Papillomavirus Vaccine and Postural Orthostatic Tachycardia Syndrome: a Review of Current Literature,* 32 J. Child Neurol. 11, 956 (2017), filed as Ex. A Tab 12 (ECF No. 18-13), at 958–59, 962 (no conclusive evidence to establish causal relationship between POTS and HPV vaccine; discussing Blitshteyn I, Brinth, Kinoshita, and Dahan).

All of the above bears heavily on the outcome in this case—and for good reason. Special masters are directed to rely on their expertise in deciding vaccine injury cases. *Hodges v. Sec'y of Health & Hum. Servs.*, 9 F.3d 958, 961 (Fed. Cir. 1993). In performing their tasks, they gain experiential insight into what kinds of evidence are more or less probative of causation—but they also develop an understanding of the kinds of claims that do, or do not, have merit. When faced with a claim that offers the same sorts of causal theories that have been repeatedly found wanting, they reasonably apply their prior knowledge.

I have had multiple opportunities in the past to consider a comparable causal theory, and have heard numerous experts propose in prior cases that components of the HPV vaccine can initiate an autoimmune cross-reaction sufficient to impact the autonomic nervous system and cause syncopal-like symptoms. *See, e.g., McKown*, 2019 WL 4072113, at *54; *Johnson*, 2018 WL 2051760, at *24; *Combs*, 2018 WL 1581672, at *18–19; *K.L.*, 2017 WL 1713110, at *14–15. Such cases, like this one, have attempted to invoke the general concept that a form of POTS *could* be autoimmune, citing available literature (like Thieben)[24] that suggests some kind of potential autoantibody association. But I have noted in reaction that POTS cannot properly be understood to be *primarily autoimmune* in etiology (as numerous items of literature filed in this case admit) —and that even if a rare form that *is* autoimmune exists, its connection with the HPV vaccine has not been preponderantly established. *McKown*, 2019 WL 4072113, at *48 (noting the existence of

[24] Thieben is in fact one of the older items of literature allowing for the possibility of an autoimmune form of POTS, since it was published in 2007. And yet in a prior case relevant herein, one of Thieben's authors (testifying as Respondent's expert) expressly *disclaimed* the article's findings on this point, observing that his own experience clinically, since the time of Thieben's publication, had suggested to him that the proposed autoimmune link was far weaker than originally theorized. *Yalacki,* 2019 WL 1061429, at *18. Such evidence is of course not part of this record—but the finding in *Yalacki* underscores the extent to which Dr. Gibbons's expressed skepticism of autoimmunity as a driver of POTS has support in the relevant medical community.

"literature support … for the idea that one *particular variant* of autonomic neuropathy" producing POTS symptoms might be associated with a particular autoantibody, thereby suggesting autoimmunity as a plausible pathologic mechanism" in some cases of orthostatic intolerance/dysautonomia, but that it is extremely uncommon and not likely vaccine-caused). This stands as the backdrop for Petitioner's claim.

II. Petitioner Has Offered Insufficient New Evidence to Support A Determination that POTS Can be Caused by the HPV Vaccine

I acknowledge that Petitioner's experts have offered a number of more recently-published items of medical or scientific literature relevant to her causation theory. She maintains that newer studies better support a POTS-autoantibody association than was substantiated in the aforementioned older cases. Indeed, some articles filed herein more expressly propose that POTS is *likely* autoimmune. *See, e.g.*, Gunning at 9. Do these more recently-published articles provide a basis to find that POTS *could* be vaccine-caused, despite the outcome of so many prior cases? Having reviewed them closely, along with the expert reports filed in this case, I answer that question in the negative.

First, the newer items of medical/scientific literature largely supplement only one aspect of Petitioner's case: the attempt to establish the existence of a type of autoantibody that might drive *some* subset of POTS cases. This is an intriguing scientific development, and it has been the animal model created in Li II that gives it some support—although (as also noted in items like Miller) that model does not provide a robust comparison to how humans (bipedal rather than four-legged, like rabbits) experience orthostatic change upon standing. I certainly have no grounds for questioning the specific reliability of many of these articles and studies, even though Dr. Gibbons raised some fair objections about how reliable the testing used to identify the presence of these autoantibodies may be—and some, like Hineno, replicate the kind of selection bias that has caused me to give less weight to previously-published articles like Kinoshita.

What I reasonably question, however, is the scope of these articles—and the extent to which they "add up" to a preponderant showing, in the context of a claim that has repeatedly been unsuccessfully advanced. For too many unresolved issues remain to conclude it is *more likely than not* that these autoantibodies *explain* POTS in enough circumstances to meet the preponderant test applicable to the first *Althen* prong. A foundational issue is whether the anti-adrenergic autoantibodies would trigger the proposed autoimmune process leading to POTS, or whether they simply arise *in connection with an existing, ongoing disease process*. This is a significant question in the context of a vaccine injury claim, where the petitioner hopes to show that vaccination of some kind *caused* the autoantibodies to come into existence and initiate disease. If POTS has had some other initiating etiology, the significance of the presence of such autoantibodies decreases, even if they theoretically play some role in the subsequent disease process.

A related matter is whether POTS *mostly* occurs due to autoimmunity, as opposed to some physiologic deficit. Gunning's assertion to the contrary, it is *far* from agreed upon by medical science that POTS can be fully deemed an autoimmune condition, with ample explanations for POTS having nothing to do directly with an immune response. *See generally* Freeman at 48; Fu & Levine at 21. As noted above, I have in prior cases observed that at best, POTS might in a *subset* of instances be autoimmune in nature, but is not commonly (and cannot be defined to *be* an autoimmune disease, in the way other injuries in the Program, like GBS, are understood). Reliance on the autoimmune form herein may be a product of the Petitioner's awareness that the best way to show causation is to implicate an autoimmune process that a vaccine might plausibly initiate. But the rarity of vaccine injuries generally does not mean that more often than not, POTS occurring after vaccination will *also* be the rare, autoimmune form.

This raises the second deficiency presented by these newer articles. Even if a subset of POTS has an autoimmune character and origin, the more recent literature largely does not suggest the HPV vaccine can cause these autoantibodies to generate in the first place. Indeed, articles like Hineno or Gunning say little to nothing about how the autoantibodies might come into being. Certainly the wild human papillomavirus infection *itself* has not been demonstrated to have anything to do with POTS—something that need not be demonstrated to prevail, but which can serve as the bedrock for arguments involving the vaccine. *See Deshler v. Sec'y of Health & Hu. Servs*., No. 16-1070V, 2020 WL 4593162, at *18 (Fed. Cl. Spec. Mstr. July 1, 2020). (finding such proof to be unquestionably assistive of arguments that a particular vaccine might also cause the same injury, although it certainly is not a prerequisite to so arguing). Rather, for this aspect of her theory, Petitioner mostly falls back onto older items of literature that purportedly show a general association with the vaccine, like Brinth or the Blitshteyn articles, but which have been rejected as unreliable on repeated occasions, as discussed above. Otherwise, case series evidence of POTS occurring after receipt of the HPV vaccine does not merit significant weight. *See Campbell v. Sec'y of Health & Hum. Servs.*, 97 Fed. Cl. 650, 668 (2011) ("[c]ase reports do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value").

In addition, arguments about molecular mimicry driving the purported autoimmune process herein do not rise beyond plausibility and are not otherwise bulwarked by reliable scientific or medical evidence establishing that antibodies produced in response to components of the HPV vaccine might in turn initiate an autoimmune cross-reaction sufficient to adversely interact with adrenergic receptors. Much of the literature offered on this point, such as Blitshteyn I, Segal, or Dahan,[25] proposes homologous similarities between HPV vaccine components in

[25] I note also that Dahan and Segal (as well as Hineno for that matter) all have a common co-author: Dr. Yehuda Shoenfeld. Dr. Shoenfeld has not only repeatedly testified in prior Program cases, but he has offered the express opinion that POTS and/or orthostatic intolerance more generally is caused by the HPV vaccine, or others. *See, e.g.*, *Johnson,* 2018 WL 2051760, at *7–12. I have not, however, found him persuasive on this subject. *Id.* at *24-27; *see also Yalacki,* 2019 WL 1061429, at *33 (Hepatitis B vaccine and POTS; observing that "time and again, when testifying in Vaccine Program cases, Dr. Shoenfeld has readily voiced his belief about the prevalence of autoimmunity

conclusory fashion, or simply based on non-substantiated contentions about amino acid sequencing that have not been independently verified in the relevant items of literature. More broadly (and as I am forced to say over and over again in Vaccine Program cases) molecular mimicry is not a "one size fits all" theory that can reasonably be applied to *any* Program case (even if some experts wield it as such). In fact, it is relatively easy for an expert to show (using database searches)[26] that amino acid sequences in a vaccine's protein components match self-sequences found within the relevant human protein. But this does not mean that invocation of molecular mimicry in a particular case carries the day for purposes of proving a persuasive causal theory. *McKown*, 2019 WL 4072113, at *50 (citing *Devonshire v. Sec'y of Health & Hum. Servs.,* No. 99-031V, 2006 WL 2970418, at *15 (Fed. Cl. Spec. Mstr. Sept. 2006)) ("[b]ut merely chanting the magic words 'molecular mimicry' in a Vaccine Act case does not render a causation theory scientifically reliable, absent *additional evidence* specifically tying the mechanism to the injury and/or vaccine in question") (emphasis in original), *mot. for review den'd,* 76 Fed. Cl. 452 (2007)).

In finding as I do, I am not determining that the evidence against Petitioner's theory is all-encompassing. As noted, some of the more recent literature offered herein bulwarks the possibility that *some* cases of POTS are autoimmune in etiology, and that *some* autoantibodies that interfere with cardiac functioning might be involved, even if their precise role remains unelucidated. Petitioner's experts also made a number of credible points about weaknesses in Respondent's defense. For example, although I give some weight to the fact that the AAS Statement reflects a reasoned view of autonomic experts casting doubt on the strength of the HPV vaccine-POTS association, Dr. Miglis persuasively noted that this is not *itself* a study that can be evaluated, but more of an opinion piece (although ultimately Respondent's point that the majority of the relevant medical community is unpersuaded by a POTS-vaccine connection merits some weight).

But in the end, the evidence Petitioner relies on to prove the HPV vaccine can "more likely than not" cause POTS is subject to the same deficiencies and limitations I have repeatedly noted plague comparable cases—even with the more recently-published literature. It is not likely that POTS is *most commonly* caused by an autoimmune process, even if certain autoantibodies have been shown to exist in the *presence* of POTS; not enough is known about the limited circumstances in which such causality is even plausible to deem anti-adrenergic autoantibodies to likely drive

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and its unerring connection to vaccination—a view so deeply entrenched and unshakable that it often defies the very legal standards I am called to apply (especially when he is asked about the timeframe over which such autoimmunity might germinate"). While Petitioner's experts in no way displayed this level of outcome-oriented testimony that so discredited Dr. Shoenfeld, his authorial role in articles aimed at supporting contentions about vaccinations and autoimmunity provides a small additional reason to question their larger validity.

[26] In many cases, claimant's experts attempt to make this kind of showing as part of the causation theory. Yet even though it alone does not make it more likely than not that the vaccine causes the relevant cross-reaction to occur, Petitioner's experts in this case have not made any attempt to establish homology between HPV vaccine components and any self-structure where POTS might be proposed to begin (let alone that the latter was itself a reliable possibility).

pathogenesis of it, by harming the autonomic nervous system (or at least interfering with its function); and, most importantly, it has not been preponderantly demonstrated that the HPV vaccine likely causes such autoantibodies to come into existence in the first place. Petitioner's theory simply does not rise about a level of baseline plausibility—and does not add enough additional, and/or new, science to suggest otherwise. There is thus simply not enough in this record different from what has been presented to me so many times before to accept Petitioner's contentions about causation herein.[27]

III. The Record Does Not Support the Conclusion that Petitioner's POTS was Vaccine-Caused

Even if I had found that the HPV vaccine can cause POTS, the circumstances of this case would not allow me to conclude as well that Petitioner's POTS *was* likely caused by the vaccination. The most obvious weakness in this aspect of Petitioner's showing is the fact that she tested *negative* for virtually all of the anti-adrenergic or other autoantibodies deemed causal. *See generally* Ex. 48. Although I take note of the testing lag (occurring so long after vaccination) as potentially explaining a diminishment in the alleged relevant autoantibodies over time, the fact remains that under Petitioner's theory, her ongoing POTS should be corroborated by the presence of these autoantibodies—and they are absent. Indeed, there is no evidence of Petitioner *ever* possessing these autoantibodies at any prior time in her medical history.

In addition, while there is some treater speculation (in particular from Dr. Pelosi) of a vaccine relationship to Petitioner's onset of symptoms, the overall record does not suggest that treater views have ever coalesced around that idea. Otherwise, Petitioner's experience has not been shown to be consistent with an autoimmune form of POTS, unfolding due to an aberrant response to the HPV vaccine, as opposed to some other form attributable to a physiologic issue, which undoubtedly explains *most* cases of POTS. Indeed, Petitioner has not established how, or whether, an autoimmune-caused form of POTS would differ in clinical presentation from POTS attributable to deconditioning, making it further difficult on this record to say that the purportedly-autoimmune form that is the basis of Petitioner's theory occurred in this case. At bottom, other than the fact that Petitioner experienced POTS symptoms temporally after vaccination, the record does not suggest the vaccine likely caused it in this case.

[27] My determination that a preponderant showing on causation was not made is not equivalent to "raising the burden" and requiring medical certainty. There are, rather, too many holes in the existing theory to conclude that vaccination can trigger POTS. Noting these evidentiary absences is not concurrent with a demand that Petitioner prove beyond a shadow of a doubt that the HPV vaccine can cause POTS—even if these holes had been filled, it would remain *uncertain* that POTS is vaccine-caused, but I would have at least enough to go on to conclude the vaccine *likely* causes it. The evidence overall as offered (and bulwarked with more recent publications) does not cross the "more likely than not" line.

IV. This Case Was Appropriately Decided on the Papers

In ruling on the record, I am choosing not to hold a hearing. Determining how best to resolve a case is a matter that lies generally within my discretion, and although the parties have not objected to my choice of this method of adjudication, I shall explain why a hearing was not required.

Prior decisions have recognized that a special master's discretion in deciding whether to conduct an evidentiary hearing "is tempered by Vaccine Rule 3(b)," or the duty to "afford[] each party a full and fair opportunity to present its case." *Hovey*, 38 Fed. Cl. at 400–01 (citing Rule 3(b)). But that rule also includes the obligation of creation of a record "sufficient to allow review of the special master's decision." *Id*. Thus, the fact that a claim is legitimately disputed, such that the special master must exercise his intellectual faculties in order to decide a matter, is not itself grounds for a trial (for if it were, trials would be required in every disputed case). Special masters are expressly empowered to resolve fact disputes without a hearing—although they should only so act if a party has been given the proper "full and fair" chance to prove their claim.

The present claim could be, and was, resolved fairly without the need for live testimony from the experts. The parties agreed on A.F.'s diagnosis, obviating the need for testimony on that topic. The question of the HPV-POTS association has been considered multiple times in the Program, and I personally have decided many prior such cases. As a result, resolution of that matter as well could be accomplished based upon the briefs and written reports. This was not a case where live expert testimony was necessary to explain a concept, and holding a hearing would not have affected or altered the outcome. I was otherwise able to read the expert reports and filed literature, and to comprehend the theory presented, giving specific attention to some of the more recently-published items of literature.

CONCLUSION

The record does not support Petitioner's contention that the HPV vaccine she received caused her to develop POTS. I therefore must DENY entitlement in this case.

In the absence of a motion for review filed pursuant to RCFC Appendix B, the Clerk of the Court **SHALL ENTER JUDGMENT** in accordance with the terms of this Decision.[28]

[28] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment if (jointly or separately) they file notices renouncing their right to seek review.

IT IS SO ORDERED.

/s/ Brian H. Corcoran
Brian H. Corcoran
Chief Special Master